SUMMARY OF SAFETY AND PROBABLE BENEFIT

1. General Information

Device Generic Name: Transcatheter Cardiac Occlusion Device

Device Trade Name: CardioSEAL® Septal Occlusion System

Applicant's Name and Address: Nitinol Medical Technologies, Inc
27 Wormwood Street
Boston, Mass. 02210

Humanitarian Device Exemption (HDE) Number: H990005

Date of Humanitarian Use Device Designation: February 22, 1999

Date of Panel Recommendation: Not Applicable (Refer to Section 12 for discussion)

Date of Good Manufacturing Practices Inspection: May 27, 1999

Date of Notice to the applicant: SEP 28 1999

2. Indications for Use

The CardioSEAL Septal Occlusion System is authorized by Federal (USA) law as a Humanitarian Use Device for use in the following indication only:

> Patients with a complex ventricular septal defect (VSD) of a significant size to warrant closure, but that based on location, cannot be closed with standard transatrial or transarterial approaches.

The effectiveness of this device in this indication has not been demonstrated.

3. Device Description

The CardioSEAL Septal Occlusion System consists of two primary components:

- The CardioSEAL, which is constructed of a metal (MP35N) framework to which polyester fabric is attached, and

- The Delivery Catheter, a coaxial polyurethane catheter designed specifically to facilitate attachment, loading, delivery and deployment of the CardioSEAL to the defect.

4. Contraindications

Presence of thrombus at the intended site of implant, or documented evidence of venous thrombus in the vessels through which access to the defect is gained.

Active endocarditis, or other infections producing a bacteremia.

Patients whose vasculature, through which access to the defect is gained, is inadequate to accommodate the appropriate size sheath.

Patients whose defect is too small to allow the 11 F sheath to cross the defect.

Anatomy in which the CardioSEAL size required would interfere with other intracardiac or intravascular structures, such as valves or pulmonary veins.

Patients with coagulation disorders who are unable to take Aspirin, Heparin, Coumadin, or other anticoagulants.

5. Warnings and Precautions:

See Warnings and Precautions in the final labeling (Information for Use).

6. ADVERSE EVENTS

6.1 Observed Adverse Events:

A total of 63 patients requiring closure of a VSD were enrolled in a 292 patient multi-center High risk study.

Four patients died within 4 months of device placement, for an overall mortality rate of 7.7% among patients receiving a device to occlude a ventricular septal defect. All four deaths were reviewed by an independent Safety and Data Monitoring Committee. One of the deaths in a small infant was classified as due to the catheterization procedure. In this patient, the cardiac catheterization procedure was complicated by complete heart block induced by the catheters. Two days after the procedure, the patient was taken to the operating room for placement of a pacing wire. During this procedure the patient suffered a cardiac arrest and could not be

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resuscitated. The remaining three deaths were attributed to the patient's underlying cardiac (2) or medical (1) condition.

A total of 194 adverse events were recorded among the 63 patients enrolled in the study for closure of their VSD. These adverse events were classified as Serious (23), Moderately Serious (75), Not Serious (92), or Unknown Seriousness (4) and were linked to either the device, the implant procedure, the catheterization procedure, or other causes, such as a pre-existing condition. Adverse events (71) that were classified as Serious or Moderately Serious and definitely or probably related to the device, the implant procedure or the catheterization are shown in Table 1.

[illegible]				
	Moderately Serious		Serious	
	Early Event*	Late Event**	Early Event*	Late Event**
Device Related				
Device Malposition	1	0	0	0
Ventricular premature beats	1	1	0	0
Endocarditis	1	0	0	0
Hemolysis	1	0	0	0
Ventricular tachycardia	3	0	0	0
Supraventricular tachycardia	1	0	0	0
Non-sustained ventricular tachycardia	1	0	0	0
Implant Procedure Related				
Arterial pulse loss, requiring heparin	1	0	0	0
Atrial flutter	1	0	0	0
Blood loss requiring transfusion	0	0	1	0
Congestive heart failure	1	0	0	0
Air embolism	1	0	0	0
Heart block (3^0)	0	0	5	0
Hypotension requiring intervention	1	0	1	0
Perforation of the heart	1	0	0	0
Transient bradycardia	0	1	0	0
Valve regurgitation-aortic	0	0	1	0
Valve regurgitation-mitral	2	2	0	0
Valve regurgitation-tricuspid	1	0	0	0
Venous thrombosis (suspected)	1	0	0	0
Ventricular tachycardia	1	0	1	0

Adverse Events [illegible]				
	Moderately Serious		Serious	
	Early Event*	Late Event*	Early Event*	Late Event*
Catheterization Procedure Related				
Acute renal failure	0	0	1	0
Blood loss requiring transfusion	13	0	0	0
Cyanosis	1	0	0	0
Fever	2	0	0	0
Heart block (3 ^{0})	0	0	1	0
Hypotension requiring intervention	6	0	0	0
Multi organ failure	0	0	1	0
Perforation of vessel	1	0	0	0
Phlebitis	1	0	0	0
Pseudoaneurysm	1	0	0	0
Pulmonary edema	1	0	0	0
Respiratory insufficiency	2	0	0	0
Sinus tachycardia	1	0	0	0
Stridor	1	0	0	0
Hypercyanotic episode	1	0	0	0
Upper respiratory infection	1	0	0	0
Ventricular tachycardia	0	0	2	0
Wheezing	1	0	0	0

* = Early event is ≤ 30 days from implant. Total =67 early events.
** = Late event is > 30 days from implant. Total =4 late events.

6.2 Potential Adverse Events:

Placement of the CardioSEAL involves using standard interventional cardiac catheterization techniques. Complications commonly associated with these procedures include, but are not limited to:

- Air Embolus
- Allergic dye reaction
- Anesthesia reactions
- Apnea
- Arrhythmia
- Death
- Fever
- Headache / Migraines
- Hematoma and/or Pseudoaneurysm including blood loss requiring transfusion

Hypertension; Hypotension
Infection including Endocarditis
Perforation of Vessel or Myocardium
Stroke / Transient Ischemic Attack
Thromboemobolic events
Valvular regurgitation.

Fractures of the framework have been reported in some implanted patients. The risk of fracture appears to be related to the size of the Occluder selected relative to the size of the heart chamber it was implanted in. Two reports of palpitations have been the only complications observed with the CardioSEAL Septal Occluder. These complications did not occur in the VSD population. In the independent, multicenter clinical trial sponsored by Children's Hospital, Boston, Massachusetts, the arm fracture rate was 18.1% in the Ventricular Septal Defect population

6.3 Observed Device Malfunctions:

There were three reports of a delivery system malfunction in which the physician had difficulty releasing the implant from the delivery catheter, one report of a kink in the delivery system, identified during the device placement, and three reports of a kink in the delivery system during loading of the device. There were no clinical sequelae associated with any of these device malfunctions.

7. Alternative Practices and Procedures

Alternative treatments for VSDs that cannot be closed through the standard transatrial or transarterial surgical approaches include medical management and/or pulmonary artery banding. In select patients, defects located in the apical portion of the heart may be surgically closed.

8. Marketing History

The CardioSEAL Septal Occlusion System has received the CE mark for marketing in Europe. Since 1997 approximately 1600 devices have been sold in the European Community, Latin America, and certain Pacific Rim countries. The CardioSEAL has been used for the treatment of a variety of defects including VSDs.

The CardioSEAL has not been withdrawn from marketing for any reason related to the safety or effectiveness of the device.

9. **Summary of Preclinical Studies**

9.1 Biocompatibility Testing

Biocompatibility testing of the implant and delivery system was shown to be acceptable by the following tests which were performed in accordance with the provisions of the ISO 10993-1 and Good Laboratory Practice (GLP) Regulations, 21 CFR 58:

Hemolysis	Cytotoxicity
Systemic Toxicity	Pyrogenicity
Intracutaneous Toxicity	Sensitization

Additional testing of the CardioSEAL included a 7-day Muscle Implant test and an Ames Mutagenicity Assay. The delivery system was also tested for Thromboresistance, Coagulation: Plasma Recalcification Time and Complement Activation. The results of this additional testing found that the implant material was non-toxic and non-mutagenic and the delivery system material was non-thrombogenic and does not activate complement.

9.2 Bench Testing

9.2.1 CardioSEAL – Bench Testing

1. Chemical analysis – MP35N wire

A chemical analysis was conducted to verify the material composition for all of the components of the permanent implant, specifically the MP35n, polyester fabric, solder, polyester suture, and platinum wire. All of these materials were tested and met their raw material specifications.

2. Mechanical Properties – MP35N wire

   Testing was conducted to determine conformance of the MP35N wire to specifications and the corrosion resistance of the wire.

   a) Tensile strength/Elongation
      Tensile strength and elongation was tested on 124 MP35N wire samples (60 as received and 64 annealed). All samples met the specifications for these characteristics.

   b) Corrosion Resistance
      To evaluate the susceptibility of the CardioSEAL to stress corrosion cracking, 27 spring arm subassemblies were subjected to static deflections in simulated body fluids. Nine samples were exposed to these conditions out to 6, 9 and 12 months. Scanning electron microscope analysis of the test samples found no evidence of stress corrosion cracking after an exposure of up to 12 months.

3. Mechanical Testing – CardioSEAL

A summary of the bench testing conducted to evaluate the performance of the CardioSEAL is provided in Table 2.

Table 2: Summary of CardioSEAL Testing

Test	Sample Size	Specification	Results
Fatigue Testing:			
Accelerated Life Testing (Springarm)	N=48 (40mm)	Must withstand 10 yrs. Equivalent (pediatric heart rate) of *in vitro* fatigue cycle testing with no fractures.	No fractures occurred in 630 million cycles.
Other Mechanical Testing:			
Arm/Body Joint Strength	N= 14	10 lbs min	Mean = 25.66lbs S.D. 2.02lbs
Ball/Body Joint Strength	N=21	8 lbs min	Mean = 10.21lbs S.D. = 0.74lbs
Arm/Fabric Strength	N=30	1 lb min	Mean = 4.23lbs S.D. 0.70lbs
Dislodgement Resistance	N=10 (17mm) N=20 (40mm)	Force required to pull an occluder out of a circular hole (50% of the size of the occluder) must be 38 grams minimum.	17mm = Mean = 169.7g S.D. 13.07g 40mm= Mean = 54.10g S.D. = 3.70g
MRI Compatibility			
MRI Compatible	5 Implants	MR safe up to 1.5 Tesla	Non-ferromagnetic Generated artifact < the size of the implant with 1.5 Tesla

A finite element analysis (FEA) was also performed to compare the springback of the model with the laboratory springback testing, determine the stresses (static and dynamic) during the loading cycle and deployment, and compare the model's fatigue prediction with spring arm fatigue test data.

9.2.2 Delivery Catheter - Bench Testing

To demonstrate the strength of the bonded joints and their ability to resist failure, tensile testing was performed on a minimum of 10 samples for each of the bonded locations. The results found that the strength of each of the bonded joints exceeded the test specification.

9.2.3 CardioSEAL Septal Occlusion System - Bench Testing

A summary of the bench testing conducted to evaluate the performance of the CardioSEAL occluder loaded on the delivery catheter is provided in Table 3.

Table 3: Summary of CardioSEAL Septal Occlusion System Testing

Test	Samples Tested	Specification	Results
Load and Deployment			
Minimum side length	17mm N=136 23mm N=88 40mm N=120	17mm: 10.4 mm min. 23mm: 14.0 mm min. 40mm: 24.4mm min.	17mm: Mean= 2.54mm SD=0.61mm 23mm: Mean= 16.42mm S.D. = 0.55mm 40mm: Mean=27.98mm S.D.=0.69mm
Force into Loader	17mm N=17 23mm N=11 40mm N=15	5 lbs max (applies to all sizes)	17mm: Mean = 0.93lbs S.D. = 0.35lbs 23mm: Mean = 1.14lbs S.D. = 0.36lbs 40mm: Mean = 1.11lbs. S.D.-0.43lbs.
Force into Pod	17mm N= 17 23mm N=11 40mm N=15	6 lbs max (applies to all sizes)	17mm: Mean= 1.43 lbs S.D. = 0.46lbs 23mm: Mean= 1.74lbs S.D. = 0.61lbs 40mm: Mean=2.46lbs. S.D.=0.58lbs.
Force out of Pod	17mm N= 17 23mm N=11 40mm N=15	8 lbs max (applies to all sizes)	17mm: Mean= 1.33lbs S.D. = 0.49lbs 23mm: Mean= 1.64lbs S.D. = 0.30lbs 40mm: Mean=2.61lbs S.D.=0.62lbs
Springback gap	17mm N= 68 23mm N=44 40mm N=60	After being subjected to a loading and deployment cycle, the distance between the proximal and distal sides must be ≤4mm. (applies to all sizes)	17mm: Mean = 0.25mm S.D. = 0.40mm 23mm: Mean= 0.015mm S.D. = 0.098mm 40mm: Mean=0.04mm S.D.=0.28mm
Ball to Ball Strength	N=30	6 lbs min (applies to all sizes)	Mean= 9.22lbs S.D. = 0.68lbs

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9.3 Sterility and Shelf Life Qualification Studies

The method of sterilization for both the CardioSEAL and delivery system is 100% ETO. The product may be sterilized no more than twice and is validated to achieve a SAL of 10^{-6} using method C of the International Document #ISO 11135, 1994 (adopted by the Committee for the Advancement of Medical Instrumentation.).

To support a 4 year shelf life, the sterility and integrity of CardioSEAL and delivery catheters, aged out to 4 years (real-time plus accelerated aged) was tested. This involved testing both the packaging and the device.

Shipping tests in accordance with the ASTM D4169, ISTA 1A tested the packaging of the CardioSEAL and delivery catheters. All packages were found intact without evidence of physical damage. Fifteen packages each of CardioSEAL devices and delivery catheters were burst tested and found to be within the test specification.

Sterility testing was conducted on 6 samples each of the CardioSEAL and delivery catheter. All samples were found to be sterile. Bond strength and functionality testing were conducted on 5 to 20 samples real time and accelerated aged out to 4 years and exposed to shipping stresses. All test results indicate that the product performs within specification and that sterility is maintained over a period of four years.

9.4 Animal Testing

Following successful initial acute studies, three chronic animal studies were conducted to evaluate the CardioSEAL using both sheep and dog models. Explants occurred at the following timepoints: 2 weeks, 30 days, 90 days, 6 months, 1 year, and 2 years. Atrial septal defects were created either via blade septostomy or Brockenbrough followed by balloon dilation. In the first study, oversized devices were placed in freshly created defects, which resulted in thrombosis and a device arm fracture. It was later confirmed that devices implanted in freshly created defects had higher levels of protein deposition and thrombosis.

The next two studies were conducted in both the sheep and dog model with defects created a minimum of 2 weeks prior to device implantation. These both resulted in an acceptable histological response. One arm fracture occurred at 30 days in a device, which did not appear to be appropriately placed within the ASD. Friction lesions were noted acutely near the suture coil location of arms not yet healed to the septal wall surface; these healed over time. The 3 month, 6 month, 1 year, and 2 year explants showed good fibrous tissue overgrowth and endothelialization with no recent thrombosis or arm fractures.

10. CLINICAL STUDIES:

Study Design/Objective: The multi-center clinical trial conducted by Children's Hospital, Boston, Massachusetts, is a prospective, non-randomized trial studying the use of the CardioSEAL® Septal Occlusion system to close a variety of hemodynamically significant defects. The risks of surgical closure for the patients enrolled in this trial were considered sufficient to justify the known and potentially unknown risks of transcatheter closure with the CardioSEAL device. The study (referred to as the High-risk study) is ongoing and is summarized below. Data from patients undergoing VSD closure were extracted from this study.

Patient Entry: Patients were eligible for enrollment in the High risk study if they had a defect(s) of sufficient size to require closure, but were considered to be at high risk for surgical closure, due to either complex medical or cardiac disease. An independent peer review group determined whether a patient should be enrolled into the trial based on the following criteria:

- the patient had a type of defect that was technically difficult or impossible to close surgically, such that the surgical risks were sufficient to justify the known and potential unknown risks of the device, or

- the patient's overall medical condition was such that the surgical risks were sufficient to justify the known and potential unknown risks of the device.

Methods: After enrollment, patients underwent cardiac catheterization. Position and size of the defect were confirmed by angiography. A hemodynamic assessment was performed pre-implant, and after test occlusion of the defect with a balloon. When these data suggested that the defect contributed to unfavorable hemodynamics and was feasible for transcatheter closure, device placement proceeded. Patients received aspirin, 1mg/kg/day, rounded to the nearest half tablet of 80 mg size, for at least six months following the procedure.

Patients were seen for follow up assessments as described in Table 4:

Timing of Evaluations - Table 4						
	Pre-Implant	Pre-D/C	1 month F/U	6 month F/U	12 month F/U	24 month F/U
Cardiac HX/PE	X	X	X	X	X	X
Chest X-Ray	X	X	X	X	X	
Fluoroscopy				X		X
Echo/Doppler	X	X	X	X	X	X
O_2 Saturation	X	X	X	X	X	X
Clinical Status Evaluation	X	X	X	X	X	X
EKG (rhythm)	X	X	X	X	X	X
Severity of illness	X	X	X	X	X	X

Primary Endpoints: A 5-category ordinal scale (Severity of Illness scale) was used to measure clinical status. Patients were grouped by their physiologic condition into three broad classes (right to left shunt, left to right shunt, or valvular/paravalvular leak). The scale took values from 1 to 5, and was constructed so that an improvement by one category (e.g., from category 1 to category 2, or from 2 to 3) would be considered clinically meaningful (refer to Table 5). Any patient who died during the study would receive a value of 0. Data used in the construction of the scale were measured objectively by diagnostic laboratory tests, documented clinical status, or echocardiography. The data were collected prospectively before device implantation, at discharge from the hospital, and at each follow-up visit, so that patient classification at each time point could be implemented using a computer algorithm.

The major criteria by which severity was categorized for patients undergoing device placement for VSD closure was left to right shunting. The Severity of Illness scale for VSDs is shown in Table 5.

Severity of Illness Scale - Table 5					
Physiologic Condition	**1**	**2**	**3**	**4**	**5**
L → R shunt	More than small residual flow <u>and</u> dependent on ventilator, balloon pump, <u>or</u> left ventricular assist device	More than small residual flow by Doppler <u>and</u> Requires IV inotropes <u>or</u> NYHA Class III <u>or</u> IV	More than small residual flow by Doppler	Small residual flow by Doppler	Trivial to absent residual flow by Doppler

[1]A deceased patient is rated as 0 on the Severity of Illness Scale.

Clinical Status Scale

The Clinical Status Scale was developed to improve ability to discriminate clinically important changes among patients. While the Severity of Illness scale grouped patients into three broad classes of physiologic condition, the Clinical Status Scale grouped patients into seven different categories (right to left shunt, left to right shunt, systemic embolic, hemodynamic compromise not due to shunt, arrhythmia, elevated PVR, and medical illness). A patient could be placed in multiple categories of the clinical status scale, as applicable to their physiologic condition.

The left to right shunt category was the category most closely related to the patient's indication for device closure of the VSD. This scale is shown in Table 6.

Clinical Status Scale - Table 6						
Category	**0**	**1**	**2**	**3**	[illegible]	**5**
L to R shunt	Ventilator dependent and/or intractable CHF	Heart failure, symptomatic	Left ventricular volume overload, significant/ large shunt	Moderate shunt	small shunt	trivial or no shunt

[2]A deceased patient is rated as -1 on the Clinical Status Scale.

Patients with prior placement of a pulmonary artery band to limit the degree of left to right shunting are categorized, where possible, according to the estimated anatomic size of the defect.

Additionally an assessment of the echocardiographic closure status was made at each time point both at the evaluating facility, and by an unaffiliated core laboratory. Residual flow was assessed using Doppler color flow mapping, and graded using the following guidelines:

"**Trivial" to "Absent"**: barely detectable or no detectable residual color flow through the defect. If flow is present, it is a single color flow jet, well-circumscribed, with a proximal jet width measuring less than 1 mm in diameter in all views.

"**Small"**: single color flow jet, well-circumscribed, and measuring 1-2mm (maximal proximal width) in all views in infants and children weighing less than 20 kg, or between 1 and 3 mm in diameter in larger children and adults.

"**More than small"**: single color flow jet, well-circumscribed, measuring greater than 2 mm in diameter in all views in infants and children weighing less than 20 kg, or greater than 3 mm in diameter in all views in larger children and adults.

Results: At the time the VSD data was analyzed, 63 patients with no additional anatomic lesions were enrolled in the study for closure of a VSD. Enrollment occurred at one investigational site. Ten of these patients did not have a device implant attempted because the defect was smaller than anticipated.

Device placement was successful in 52 of 53 patients (98.1%) in whom an implant was attempted. One patient had an unfavorable anatomy which precluded device placement. Multiple procedures were performed in 7 patients, and multiple devices were implanted in 24 patients for a total of 98 implanted devices. None of the devices embolized.

The types of VSD defects closed with a CardioSEAL device were: congenital muscular (25); post-operative (24); and post-infarction (3). Sixteen patients (25.4%) had previously undergone placement of a pulmonary artery band; 4 had been debanded.

Among the 52 patients treated with a CardioSEAL device, there were 20 (38.5%) males and 32 (61.5%) females. The age of the patients ranged from 0.3 years to 79 years, with a median age of 4.4 years.

Three devices were explanted, 2 at the time of a heart transplant, and 1 during a Fontan surgery performed after a failed septation.

The following tables present the combined results of the effectiveness measures for all VSD defect types. The available data column presents the number of patients with data available (numerator) and the number of patients who were expected to be seen at the respective visits (denominator).

Table 7 reflects the number of patients observed within each Severity of Illness category at each visit.

Severity of Illness – Table 7							
		Category					
Time point	**0**	**1**	**2**	**3**	**4**	**5**	**Available Data**
Initial	0	3	6	26	10	0	45/50
Discharge	0	1	1	5	15	14	36/48
1 Month	2	0	0	1	11	19	33/47
6 Month	2	0	1	1	13	13	30/40
12 Month	0	0	0	3	5	8	16/31
24 Month	0	0	0	0	2	8	10/10

Table 8 reflects the number of patients observed within each Clinical Status category at each visit.

		Clinical Status –Table 8						
		Category						
Time Point	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**Available Data**
Initial	0	5	13	10	21	3	0	52/52
Discharge	0	1	2	1	6	25	12	47/48
1 Month	2	0	0	0	3	23	13	41/47
6 Month	2	0	0	1	0	18	11	32/40
12 Month	0	0	0	0	1	16	7	24/31
24 Month	0	0	0	0	1	6	7	14/14

Table 9 reflects the number of patients observed within each Echo closure category at each visit.

Echo Closure Status – Table 9				
		Category		
	None - Trivial	**Small**	**More than small**	**Available Data**
Initial	0	10	37	47/52
Discharge	15	13	5	33/52
1 Month	19	10	2	31/50
6 Month	15	14	1	30/41
12 Month	11	4	2	17/32
24 Month	7	2	0	9/9

11. Conclusions Drawn from the Studies

The pre-clinical studies indicate that the CardioSEAL Septal Occlusion System is biocompatible and has the appropriate physical and performance characteristics for its intended use, as stated in the labeling.

The clinical data generated from the High-risk study at Children's Hospital, Boston, Massachusetts indicates patients will not be exposed to an unreasonable or significant risk of illness or injury, and that the probable benefit to health from the use of the device outweighs the risk of injury or illness, taking into account the probable risks and benefits of alternative forms of treatment.

The preclinical studies and the clinical data from the High-risk study provide reasonable assurance of the safety and probable benefit of the CardioSEAL Septal Occlusion System when used in accordance with its labeling.

12. Panel Recommendations

A Circulatory System Devices Panel advisory meeting was not held to discuss this device. However, a general Panel meeting was held on October 24, 1997, where a lengthy discussion of clinical requirements for this category of devices, i.e., occlusion devices intended to treat congenital heart disease, took place. Based on a review of these recommendations and the data in the HDE, it was determined that a Panel meeting was not necessary for this device.

13. FDA Decision

CDRH determined that, based on the data submitted in the HDE, the CardioSEAL Septal Occlusion System will not expose patients to an unreasonable risk of illness or injury, and the probable benefit to health from using the device outweighs the risk of illness or injury, and issued an approval on SEP 28 1999

14. Approval Specifications

Indications for Use: See the Instructions for Use (Attachment 1)

Hazards to Health from Use of the Device: See CONTRAINDICATIONS, WARNINGS and PRECAUTIONS, and ADVERSE EVENTS in the Instructions for Use (Attachment 1)